

Phthalates in Prescription Drugs Some Medications Deliver High Doses

Until recently, most of the concern surrounding the health risks of phthalates has focused on the use of these plasticizers in toys, personal care products, food packaging, and medical equipment such as intravenous tubing. A case report in 2004 raised the possibility that certain prescription medications may also be a source of phthalate exposure for some people [*EHP* 112:751–753 (2004)]. That finding prompted a systematic investigation that links phthalate-containing medications with high internal exposure to these chemicals [*EHP* 117:185–189; Hernández-Díaz et al.].

The 2004 case study pinpointed Asacol®, a medication for treating ulcerative colitis, as a probable source of phthalate exposure. Asacol is covered with an enteric coating of dibutyl phthalate (DBP) that prevents the medication from degrading before it reaches the small intestine. Concentrations of the main metabolite of DBP in the urine of the case study subject corresponded to an uptake of DBP exceeding by two orders of magnitude the 95th percentile reported by the Centers for Disease Control and Prevention in the general population. The concentrations also surpassed the reference dose established for DBP by the U.S. Environmental Protection Agency (EPA) on the basis of animal testing.

To assess possible links between phthalate-containing prescription medication usage and excreted metabolites, the investigators searched National Health and Nutrition Examination Survey (NHANES) data from survey periods between 1999 and 2004 when urine

samples were tested for phthalate metabolites and participants were asked about their use of prescription medications. Various enteric-coated medications identified as likely to contain phthalates included mesalamine (the generic form of Asacol), didanosine (an antiretroviral agent), omeprazole (which inhibits gastric acid secretion), and theophylline (used to treat asthma and other lung diseases).

Among the 6 documented mesalamine users, average urine concentrations of DBP metabolites were 50 times higher than those of nonusers. For 2 of the 6 mesalamine users, the DBP metabolite concentrations pointed to uptake exceeding the EPA's reference dose. Users of the other phthalate-containing medications also had significantly higher concentrations of some metabolites than did nonusers, though the gaps between users and nonusers were considerably smaller than for mesalamine. The NHANES data also showed that at least 3 women who reported taking phthalate-containing medications were pregnant.

These findings call for more investigation, the authors write, particularly because some phthalates cross the placenta and cause reproductive and developmental effects in laboratory animals. In one study of male infants, increasing prenatal exposure to background levels of phthalates was associated with a decrease in the distance between the anus and base of the penis, indicating incomplete male reproductive development [*EHP* 113:1056–1061 (2005)]. The authors of the new study write that phthalate-containing medications are among some of the most widely prescribed drugs in the United States, which implies that many people, including pregnant women, may be exposed to high concentrations of phthalates. —Kellyn S. Betts

Double Trouble Flu Intensifies Effects of Ozone

Environmental health scientists have long speculated that the influenza virus could intensify the pulmonary effects of air pollution or vice versa. Like air pollution, influenza affects primarily the respiratory system, and ambient air pollutants may either lower resistance to viral infection or provide a vehicle that facilitates the spread of the virus, or both. There have been a number of laboratory-based animal studies on this potential relationship but no epidemiologic research. Researchers at the University of Hong Kong, in the first study of the influenza–air pollution interaction in humans, now report that respiratory hospitalizations and mortality significantly increased when ozone (O₃) levels rose during flu season [*EHP* 117:248–253; Wong et al.].

The authors conducted a retrospective population-based study focusing on hospitalization and mortality rates for respiratory and cardiovascular disease. Medical data on patients diagnosed with respiratory or cardiovascular disease between 1996 and 2002 came from 14 Hong Kong hospitals. The authors determined “influenza intensity” during the same period as the percentage of respiratory specimens that tested positive for influenza each week. The Hong Kong Environmental Protection Department provided data on average daily concentrations of nitrogen dioxide (NO₂), sulfur dioxide (SO₂), particulate matter smaller than 10 µm (PM₁₀), and O₃.

As O₃ levels increased during times of high influenza intensity, so did the number of hospitalizations and deaths from respiratory disease. The association was stronger in women than men, the researchers reported. There was no significant relationship between O₃ and cardiovascular disease hospitalizations or mortality, and the data reflected no significant modification by influenza on the health effects of the other pollutants studied. Hong Kong has two flu seasons, peaking in January–February and May–July. O₃ levels in Hong Kong typically peak in the sunniest months of September–December, when ultraviolet radiation reacts with nitrogen oxides and volatile organic compounds to form the noxious gas.

A surprising finding was a decrease in hospitalization for respiratory illness when peak PM₁₀ concentrations coincided with flu outbreaks, whereas PM₁₀ increases at other times were associated with increased hospitalizations. The researchers hypothesize that PM₁₀ may diminish the flu effect by limiting the amount of ultraviolet light entering the atmosphere, which in turn would reduce the production of ozone.

The authors found weak interactions between influenza and both NO₂ and SO₂, but cautioned against drawing conclusions about individual pollutants that react in the atmosphere. NO₂, for example, can combine with oxygen to form O₃. The researchers propose that future studies focus on influenza's potential interactions with a combination of pollutants in the atmosphere. —Cynthia Washam



Influenza appeared to exacerbate the health effects of ozone pollution in Hong Kong.

Trumped Treatment? BPA Blocks Effects of Breast Cancer Chemotherapy Drugs

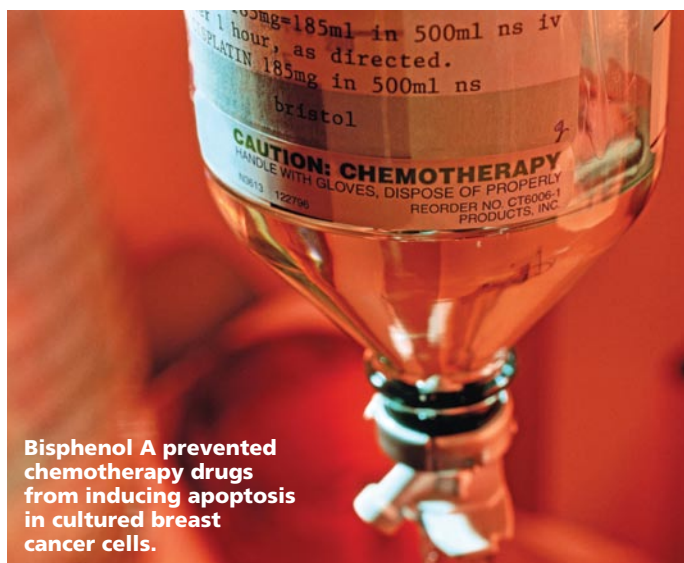
Widespread human exposure to the chemical bisphenol A (BPA) has resulted from its use in a diverse array of consumer products. Research on the potential health effects of BPA has focused on the chemical's ability to mimic or block natural estrogen. In animal studies, prenatal exposure to BPA increased susceptibility to mammary cancer in adulthood. However, studies of adult animals and cell cultures have had mixed results, and even less certain is how BPA might influence established breast cancer and its treatment. A new cell culture study is the first to show that BPA, at concentrations comparable to those found in the general population, reduces the efficacy of chemotherapy drugs in breast cancer cells, apparently by altering expression of proteins involved in apoptosis, or programmed cell death [*EHP* 117:175–180; LaPensee et al.].

The study used estrogen-responsive T47D cells and estrogen-insensitive MDA-MB-468 cells. Cells were pretreated with BPA and then incubated alone or with one of several concentrations of added doxorubicin, cisplatin, or vinblastine, commonly used chemotherapy drugs. BPA concentrations (1 and 10 nM) were comparable to levels documented in human milk and blood (0.5–40 nM). In some experiments, BPA pretreatment was preceded by addition of either ICI or PHTPP,

compounds that block classical estrogen receptor- α and - β (ER α and ER β , respectively). In addition to assessing cell survival, the researchers determined genetic expression and concentrations of the antiapoptotic proteins Bcl-2, Bcl-xL, and survivin, as well as classical and nonclassical estrogen receptors.

The researchers found in T47D cells that BPA partially or completely blocked the effects of all doses of doxorubicin and cisplatin but only the lowest dose of vinblastine, with similar results in MDA-MB-468 cells. BPA by itself bolstered cell viability (i.e., chemoresistance) in T47D cells but not in MDA-MB-468 cells. Neither ICI nor PHTPP affected the ability of BPA to block doxorubicin's actions in T47D cells, and BPA was able to mediate the drugs' effects in MDA-MB-468 cells. These observations together suggest that BPA does not act via ER α or ER β , helping to account for its effects on ER-insensitive cells.

Given previous research that demonstrates a high binding affinity of estrogen-related receptor- γ (ERR γ) to BPA [*EHP* 116:32–38 (2008)], the researchers speculate that ERR γ , expressed by both cell lines in their study, is the most likely target for BPA binding. Based on their finding that BPA combined with doxorubicin increased levels of Bcl-2 and Bcl-xL, the researchers conclude that derailment of apoptosis could be a mechanism—perhaps common to all three drugs—by which BPA may inhibit the efficacy of breast cancer drugs. Both BPA binding to ERR γ and the compound's role in apoptosis should be further examined in future research. —Julia R. Barrett



Bisphenol A prevented chemotherapy drugs from inducing apoptosis in cultured breast cancer cells.